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(21) International Application Number: PCT/US88/02131 (22) International Filing Date: 23 June 1988 (23.06.88) (31) Priority Application Number: P 37 21 574.4 (32) Priority Date: 30 June 1987 (30.06.87) (33) Priority Country: DE (71) Applicant: RIKER LABORATORIES, INCORPORATED [US/US]; Building 225-1N-07, 3M Center, Saint Paul, MN 55144-1000 (US). (72) Inventors: ZERBE, Horst-Georg ; BECKER, Jorn, Ullrich ; Kettelhack Riker Pharma GmbH, Wilbecke 12-14, P.O. Box 1340, D-4280 Borken 1 (DE).		(74) Agents: SPRAGUE, Robert, W. et al.; Minnesota Mining and Manufacturing Company, P.O. Box 33427, Saint Paul, MN 55133-3427 (US). (81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PELLETS WITH ENZYMATICALLY CONTROLLED DRUG RELEASE (57) Abstract Pharmaceutical compositions in pellet form with enzymatically controlled release of the pharmaceutical substance are described which comprise a core and an envelope layer surrounding said core. The core contains the pharmaceutical substance, an enzyme and a substrate for the enzyme. The envelope layer contains a water-insoluble film-forming macromolecular substance and a water-soluble pore former.		

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PELLETS WITH ENZYMATICALLY CONTROLLED DRUG RELEASE

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Field of the Invention

10 The present invention relates to a pharmaceutical composition in pellet form with enzymatically controlled release of the pharmaceutical substance.

Background of the Invention

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 In many cases, pharmaceutical substances are administered to patients as pharmaceutical compositions with so-called sustained release. After the patient has taken the pharmaceutical composition, the pharmaceutical substance is released in the gastro-intestinal tract slowly over several hours. In this way, the frequency of administration of the pharmaceutical composition, which in many cases the patient considers annoying, can be reduced. At the same time, the sustained release of the pharmaceutical substance prevents plasma level peaks and undesired side effects may result from fast resorption.

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 The sustained release of the pharmaceutical substance can be achieved for instance by mixing the pharmaceutical substance with a water-insoluble carrier and compressing it into tablets. Suitable carrier materials are cellulose derivatives, waxes, synthetic materials, such as polyvinylchloride, polyvinylacetate, polyethylene or differently substituted polymethacrylic acid derivatives. Other water-insoluble polymers are known to the expert. The release of the pharmaceutical substance can also be retarded by mixing the pharmaceutical substance with hydrophilic macromolecules and compressing the mixture into tablets. Such substances are also known to the expert.

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Examples are gum arabic, cellulose derivatives, water-soluble polyacrylic acid derivatives, polyvinyl pyrrolidone, tragacanth or guar.

5 In both cases so called matrix systems are produced, from which the pharmaceutical substance, after having been administered to the patient, is released under controlled diffusion. The degree to which the release of the pharmaceutical substance is retarded essentially
10 depends on the quantitative ratio of the pharmaceutical substance and the polymer forming the matrix.

In another method known to the expert, the tablets, pellets or granules containing the pharmaceutical substance are coated with a lacquer layer of a film-forming
15 material that is insoluble in the gastric juice. The corresponding film formers are known to the expert. Examples of preferred film formers are ethyl cellulose, polyvinylacetate, anionic polymers of methacrylic acid and methacrylic acid esters, acrylic and methacrylic acid ester
20 copolymers, such as 1:1 methacrylic acid/methacrylate copolymers and 2:1 ethylacrylate/methylmethacrylate copolymers, shellac or mixtures of these substances. The film may additionally contain pore-forming substances which are likewise known to the expert. Polyethylene glycols,
25 polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose or mixtures of these substances are preferred. The type and amount of these additives depends on the rate at which the pharmaceutical substance is to be released.

30 All foregoing systems suffer from the disadvantage that once the patient has taken the pharmaceutical composition, the release rate of the pharmaceutical substance is subject to greater or smaller variations depending on the viscosity of the
35 gastro-intestinal content, the peristalsis or the pH value. This may, for instance, have as a consequence that the

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necessary blood level is not achieved and thus the desired therapeutic effect is not attained or that plasma level peaks are produced which may entail undesired side effects.

5 The release of the pharmaceutical substance independently from the aforementioned physiological influences can be achieved by release systems in which the release of the pharmaceutical substance is osmotically controlled. US Patent 3,916,899, for instance, describes a
10 preparation (Osmogit^R) consisting of two compartments separated by a semipermeable membrane, one of these compartments being filled with an osmotically active agent such as potassium chloride and the other compartment containing the pharmaceutical substance. After the
15 preparation has been administered to the patient, gastro-intestinal fluid diffuses into the compartment containing the osmotically active agent, whereby the solution of the pharmaceutical substance is pressed into the gastro-intestinal tract by a specific opening provided
20 for this purpose. Other embodiments of this preparation are described in US Patents 4,612,008, 4,503,030, 4,210,139 and DE-OS 33 10 096. However, the fact that after administration a highly concentrated solution of the osmotically active agent is pressed through the opening,
25 which may cause quite some side effects such as perforations of the patient's intestinal wall, constitutes a considerable disadvantage of this preparation. This is known as the so-called "cutting torch" effect.

A further disadvantage of this preparation is
30 that it is in the "single-unit" form. As such its duration of stay in the portions of the gastro-intestinal tract which are capable of absorption depends to a large degree on the individual variations in the passage times of the gastrointestinal tract. In the case of a reduced passage
35 time, the duration of the pharmaceutical compositions in those portions of the intestine which are capable of absorption is shortened so that a considerable part of the pharmaceutical substance is discharged unused.

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US Patent 3,493,652 describes the use in pharmaceutical compositions of a substrate and an enzyme disintegrating the substrate. The pharmaceutical substance is closely surrounded by the substrate which is a carbohydrate, lipid or protein whereby the release of the pharmaceutical substance is prevented. The enzyme causes the matrix to disintegrate and thus allows the pharmaceutical substance to dissolve in the gastro-intestinal juice. The structure and the principle of operation of the invention disclosed in US Patent 3,493,652, however, in the case of orally administered solid pharmaceutical compositions described therein, have the consequence that the rate of release of the incorporated pharmaceutical substance continues to depend on physiological influences, such as viscosity of the intestinal content and intestinal peristalsis, and thus may be subject to considerable individual variations.

20 Summary of the Invention

The technical problem underlying the present invention is to provide a pharmaceutical composition in pellet form comprising a core, which core contains the pharmaceutical substance, and an envelope layer surrounding the core, which minimizes the influence of the physiological factors, such as intestinal peristalsis and the viscosity of the intestinal content, on the release of the active ingredient and at the same time balances individual variations of the gastro-intestinal passage times. The problem is solved in that a) the core contains the pharmaceutical substance or a mixture of pharmaceutical substances, a pharmacologically acceptable enzyme or enzyme mixture and a pharmacologically acceptable polymer as a filler and substrate for the enzyme or enzyme mixture, and b) the envelope layer contains a pharmacologically acceptable, water-insoluble, film-forming macromolecular substance and a water-soluble pore-former.

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After administration, the pellets disperse over the gastrointestinal content, whereby the individual variations of the gastro-intestinal passage times are compensated for.

5 Apart from the pharmaceutical substance or mixture of pharmaceutical substances and optionally additional auxiliaries, the core contains in simple mixture a pharmaceutically acceptable polymer as a filler and substrate, and an enzyme or enzyme mixture for
10 disintegrating said polymer. The envelope layer contains a pharmacologically acceptable water-insoluble, film-forming macromolecular substance and a water-soluble pore-former. In order to facilitate administration to the patient, the
15 pellets are preferably filled into hard gelatin capsules of a suitable size. The purpose behind this pharmaceutical composition is that after the composition has been taken by the patient and come into contact with the gastro-intestinal fluid, the polymer is enzymatically
20 decomposed into pharmaceutically acceptable degradation products (water-soluble subunits) which are dissolved by the gastro-intestinal juice. The increase in the osmotic pressure thus produced in the interior of the pellets results in a continuous flow of the solution of the
25 pharmaceutical substance from the interior of the pellet through the envelope layer surrounding the core.

The formation of the osmotic pressure in the interior of the pharmaceutical composition of the present invention occurs independently from physiological
30 influences such as pH, viscosity and peristalsis and depends solely on the enzyme activity; the release rate being finally controlled by the outer layer surrounding the pellet of the invention.

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Brief Description of the Drawing

The invention will be better understood by
5 reference to the drawing.

The drawing is an illustration of a pellet of the invention. The core of the pellet contains the active ingredient 1, the enzyme or enzyme mixture 2, the substrate 3 and, optionally, further granulation auxiliaries. The
10 core is surrounded by the envelope layer 4.

Detailed Description of the Invention

Suitable substrate polymers in accordance with
15 the invention are substances whose enzymatic degradation leads to pharmacologically acceptable degradation products which are soluble in the gastro-intestinal juice. Examples are polyglucosides, glycogen, α -amylose, amylopectin, pullulan, laminarin, paramylum, callose, cellulose, inulin,
20 phlean, mannans, xylans, arabinans, galactomannans, chitin, chitosan, gelatin, casein or ribonucleic acid. Suitable corresponding enzymes are α -amylase, amyloglucosidase, α -glucosidase, pullulanase, β -glucosidase, cellulase, β -fructosidase, mannosidase, pectinase, chitinase,
25 proteases or ribonucleases. The combination of enzyme or enzyme mixture and substrates is chosen in such a way that the substrate is degraded to water-soluble subunits. A preferred enzyme-substrate combination is α -amylase/pregelatinized corn starch or amylose.

30 The quantitative ratio of polymer to the corresponding enzyme depends on the desired duration of release and usually ranges from 100 : 1 and 100,000 : 1. By a suitable selection of the quantitative ratio of polymer and corresponding enzyme, the duration of release
35 of the pharmaceutical substance can be controlled to range from 8 to 24 hours. The core may additionally contain granulation auxiliaries, such as soluble dextrans, polyvinyl pyrrolidone or hydroxypropyl cellulose, which are known to the person skilled in the art.

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The envelope layer surrounding the core and retarding the release of the pharmaceutical substance comprises a film-forming macromolecular substance(s) which is essentially insoluble in the gastro-intestinal juices. These are known to the expert. Ethyl cellulose with an ethoxy content of 47.5 to 49% is preferably used. Other suitable substances are hydroxypropylmethyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, acrylic acid ester, methacrylic acid ester, shellac, cellulose acetate phthalate or copolymers of neutral methacrylic acid esters. The envelope layer additionally contains pore-forming substances which are likewise known to the expert. Polyethylene glycol with a molecular weight in the range from 200 to 6,000 is particularly preferred for this purpose. Other suitable pore formers are propylene glycol, diethylphthalate, dibutylphthalate, triacetin, citric acid ester, glycerin, sorbitol or ethylene glycol. The type and quantity of these additives depend on the rate at which the pharmaceutical substance is to be released.

Pharmaceutical substances for the pharmaceutical composition in accordance with the invention are for instance antibiotics, hormones, antipyretics, antidiabetics, coronary dilators, cardiac glycosides, spasmolytics, antihypertensive agents, psychotropic agents, agents for treating migraine, corticoids, analgesics, antirheumatics, anticholinergics, sympatholytics, sympathomimetics, vasodilators, anticoagulants, or antiarrhythmics.

The drawing shows the structure of a pellet of the invention. The core contains the active ingredient 1, the enzyme or enzyme mixture 2, the substrate 3, and optionally further granulation auxiliaries.

The core is surrounded by the envelope layer 4 comprising a water-insoluble polymer(s). The envelope layer 4 additionally contains water-soluble pore-forming substances, the quantitative portion of which is from 5 to 50% of weight of the envelope layer, and which result upon ingestion in pores 5 being formed in the envelope layer.

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The pharmaceutical composition of the invention shows the following advantages:

- 5 1. The pharmaceutical substance is released from the individual pellets irrespective of the mentioned physiological influences, i.e., the pH value, gastro-intestinal motility and viscosity.
- 10 2. Variations in the gastro-intestinal passage times are compensated for by the "multiple unit dosage form" principle. This way, the reproducibility of the release of the pharmaceutical substance is improved compared to Osmogit^R preparation.
- 15 3. The substances resulting from the enzymatic degradation of the polymers are physiologically acceptable; in addition, they are not released punctiformly as in the case of the Osmogit^R preparations, but are released into the gastro-intestinal tract from the entire surface of the pharmaceutical composition. Thus a "cutting torch" effect
20 is avoided.
- 25 4. By controlling the variation in the quantitative ratio of enzyme : substrate, it is possible to control the liberation kinetics correspondingly, as the reaction rate constant of the degradation of the polymer only depends on the enzyme concentration.

The following Examples provided to illustrate the invention, but they are not intended to limit the invention.

Example 1

- 30 A pharmaceutical composition is prepared as follows: The corresponding amounts of polymer, pharmaceutical substance and enzyme are thoroughly mixed in a dry state. The mixture is then thoroughly moistened by a
35 small amount of isopropanol. The mixture is granulated with a 5% aqueous solution of hydroxypropyl cellulose (average molecular weight 100,000).

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The moist granulate so prepared is extruded by means of a hole sieve, the holes having a diameter of 1 mm. The extrudate is transferred into a suitable spheronizer and rendered round at maximum rotation. The crude pellets
5 are transferred to a fluidized bed dryer and dried in the air stream. The dried pellets are sprayed in the fluidized bed dryer with a suspension of ethyl cellulose (7 weight %), polyethylene glycol (PEG) 6000 and talcum in ethanol.

10 After application of the whole envelope layer, the pellets are dried for 30 more minutes. Finally, the pellets are filled into hard gelatin capsules by means of a suitable capsulating machine. By this process a product having the following composition is prepared:

15	<u>Ingredients</u>	<u>%</u>
	pregelatinized starch	32.68
	corn starch (native)	32.623
20	α -amylase	0.007
	hydroxypropyl cellulose	1.63
	crystal violet	
	(model substance)	1.63
	ethyl cellulose	19.70
25	PEG 6000	7.84
	talcum	3.92

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Example 2

Example 1 was repeated except for using a higher amylase
5 portion. The resulting product had the following
composition:

	<u>Ingredients</u>	<u>%</u>
10	pregelatinized starch	32.86
	corn starch (native)	32.827
	α -amylase	0.033
	hydroxypropyl cellulose	1.15
	crystal violet	
15	(model substance)	1.64
	ethyl cellulose	19.67
	PEG 6000	7.88
	talcum	3.94

20 Release of the Pharmaceutical Substance

The amount of the pharmaceutical substance
released in vitro was measured in the paddle apparatus of
USP XXI, incorporated herein by reference. For this
25 purpose, 100 mg each of the products prepared according to
Examples 1 and 2 were incubated in 900 ml of water at 37°C.
The stirring rate was 50 rpm. The amounts of
pharmaceutical substance released at the time of removing
them were determined spectrophotometrically.

30 The results are shown in Table I. The increase
in the enzyme concentration caused an increase in the
release of the pharmaceutical substance per time unit.

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Table I

Amount of released crystal violet

5	<u>Time (h)</u>	<u>Example 1</u>	<u>Example 2</u>
	0.75		9.3
	1.25	1.6	19.4
	2.0	4.2	28.0
	2.5	6.4	32.4
10	3.75	12.5	38.5
	4.75	17.5	43.2
	5.75	21.5	43.9
	6.75	23.5	44.6
15	23.0	33.1	46.9

Example 3

A pharmaceutical composition containing
20 theophyllin as a pharmaceutical substance was prepared in
accordance with example 1. Its composition is shown in
Table II.

Comparative Example

25 Another pharmaceutical composition was prepared
in accordance with Example 3, however without adding an
enzyme. The composition is also shown in Table II.

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Table II

Composition of the theophyllin-containing products.

5	<u>Ingredients</u>	<u>Example 3</u>	<u>Comparative</u>
		%	<u>Example</u>
			%
	pregelatinized starch	26.16	26.17
10	corn starch (native)	26.16	26.17
	α -amylase	0.026	-
	hydroxypropyl cellulose	1.16	1.16
	theophyllin (model substance)	5.81	5.81
15	ethyl cellulose	25.42	25.43
	PEG 6000	10.17	10.17
	talcum	5.09	5.09

20 Release of the Pharmaceutical Substance

The release of the pharmaceutical substance was also determined under the conditions stated in Examples 1 and 2. The results are shown in Table III.

25 Table III

Amount of released theophyllin

30	<u>Time (h)</u>	<u>mg released</u>	
		<u>Example 3</u>	<u>Comparative Example</u>
	2	3.41	1.70
	3	4.26	2.72
	5	5.28	3.41
35	6	5.95	3.42
	7	7.15	3.74
	8	8.16	4.42
	24	13.6	4.76

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Example 4

5 A pharmaceutical composition containing flunarizin as a pharmaceutical substance was prepared in accordance with Example 3. Its composition is shown in Table IV.

Table IV

10

Composition of a flunarizin-containing product

	<u>Ingredients</u>	<u>%</u>
15	pregelatinized starch	26.16
	corn starch (native)	26.16
	α -amylase	0.026
	hydroxypropyl cellulose	1.16
20	flunarizin (model substance)	5.81
	ethyl cellulose	25.42
	PEG 6000	10.17
	talcum	5.09

25

Example 5

A pharmaceutical composition containing salbutamol sulfate as a pharmaceutical substance was prepared in accordance with Example 4. Its composition is shown in Table V.

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Table V

Composition of a salbutamol sulfate-containing product

5		
	<u>Ingredients</u>	<u>%</u>
	microcrystalline cellulose	35.5
10	corn starch	17.75
	pregelatinized starch	10.65
	hydroxypropyl cellulose	4.15
	α -amylase	0.011
	amyloglucosidase	0.11
15	talcum	0.5147
	1:2:0.1 ethylacrylate/methyl-	
	methacrylate/trimethylaminoethyl-	
	methacrylate chloride copolymer	21.46
	propylene glycol	2.13
20	Aerosil ^R (highly dispersed	
	silicic acid)	1.086
	salbutamol sulfate	6.88

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The claimed invention is:

- 5 1. A pharmaceutical composition in pellet form comprising a core, which core contains the pharmaceutical substance, and an envelope layer surrounding the core, the composition being characterized in that
 - 10 a) the core contains the pharmaceutical substance or a mixture of pharmaceutical substances, a pharmacologically acceptable enzyme or enzyme mixture, a pharmacologically acceptable polymer as a filler and as a substrate for the enzyme or enzyme mixture, and
 - 15 b) the envelope layer contains a pharmacologically acceptable, water-insoluble, film-forming macromolecular substance and a water-soluble pore former.
- 20 2. The pharmaceutical composition according to Claim 1, wherein the combination of enzyme or enzyme mixture and substrate is selected in such a way that the substrate is degraded to water-soluble subunits.
- 25 3. The pharmaceutical composition according to Claim 1, wherein the quantitative ratio of enzyme to substrate is selected in such a way that the duration of release of the pharmaceutical substance is from about 8 to 24 hours.
- 30 4. The pharmaceutical composition according to Claim 1, wherein the substrate is polyglucoside, glucogen, amylose, amylopectin, pullulan, laminarin, paramylon, callose, cellulose, inulin, phlean, mannan, xylane, 35 arabinan, galactomannan, chitin, chitosan, gelatin, casein or ribonucleic acid or a combination thereof.

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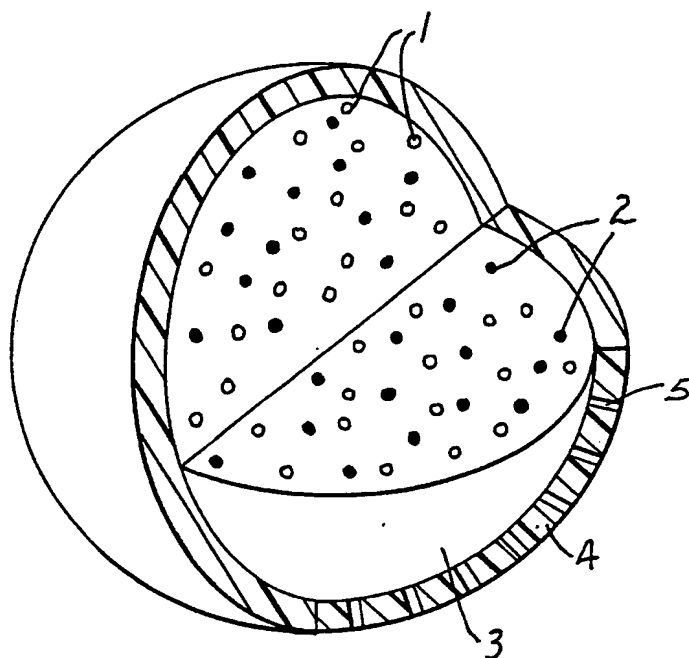
5. The pharmaceutical composition according to Claim 1, wherein the enzyme is α -amylase, amyloglucosidase, α -glucosidase, pullulanase, β -glucosidase, cellulase, β -fructosidase, mannosidase, pectinase, chitinase, protease, ribonucleases or a combination thereof.

6. The pharmaceutical composition according to Claim 1, wherein the enzyme is α -amylase and a substrate is amylose.

7. The pharmaceutical composition according to Claim 1, wherein the pharmaceutical substance is salbutamol or the sulfate salt thereof.

8. The pharmaceutical composition according to Claim 1, wherein the composition is filled in hard gelatin capsules.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US88/02131

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC: ⁴ A 61 K 9/22; A 61 K 47/00; A 61 K 37/48														
II. FIELDS SEARCHED <div style="text-align: right; font-size: small;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%; border: none;">Classification System </td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none; text-align: center; vertical-align: middle;">IPC⁴</td> <td style="border: none; text-align: center; vertical-align: middle;">A 61 K</td> </tr> </table> <div style="text-align: center; font-size: x-small; margin-top: 5px;"> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸ </div>			Classification System	Classification Symbols	IPC ⁴	A 61 K								
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; font-size: x-small;">Category ¹⁰</th> <th style="width: 70%; font-size: x-small;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; font-size: x-small;">Relevant to Claim No. ¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">Y</td> <td>US, A, 3493652 (C W HARTMAN) 3 February 1970 see the whole document cited in the application --</td> <td style="text-align: center; vertical-align: top;">1-8</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">Y</td> <td>WO, A, 8303061 (BATTELLE DEVELOPMENT CORP.) 15 September 1983 see the whole document --</td> <td style="text-align: center; vertical-align: top;">1-8</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>US, A, 4261969 (J HELLER) 14 April 1981 see claim -----</td> <td style="text-align: center; vertical-align: top;">1-8</td> </tr> </tbody> </table>			Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	Y	US, A, 3493652 (C W HARTMAN) 3 February 1970 see the whole document cited in the application --	1-8	Y	WO, A, 8303061 (BATTELLE DEVELOPMENT CORP.) 15 September 1983 see the whole document --	1-8	A	US, A, 4261969 (J HELLER) 14 April 1981 see claim -----	1-8
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<div style="display: flex; justify-content: space-between; font-size: x-small;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 50%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"Z" document member of the same patent family</p> </div> </div>														
IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"> Date of the Actual Completion of the International Search <div style="text-align: center; margin-top: 10px;">31st October 1988</div> </td> <td style="width: 50%; border: none;"> Date of Mailing of this International Search Report <div style="text-align: center; margin-top: 10px; font-size: large;">25 NOV 1988</div> </td> </tr> <tr> <td style="border: none;"> International Searching Authority <div style="text-align: center; margin-top: 10px;">EUROPEAN PATENT OFFICE</div> </td> <td style="border: none;"> Signature of Authorized Officer <div style="text-align: center; margin-top: 10px;"> P.C.G. VAN-DER PUTTEN </div> </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="text-align: center; margin-top: 10px;">31st October 1988</div>	Date of Mailing of this International Search Report <div style="text-align: center; margin-top: 10px; font-size: large;">25 NOV 1988</div>	International Searching Authority <div style="text-align: center; margin-top: 10px;">EUROPEAN PATENT OFFICE</div>	Signature of Authorized Officer <div style="text-align: center; margin-top: 10px;"> P.C.G. VAN-DER PUTTEN </div>								
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT PCT/US88/02131
ON INTERNATIONAL PATENT APPLICATION NO. SA 23462**

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3493652	03/02/70	None	
WO-A- 8303061	15/09/83	JP-A- 58189031	04/11/83
		EP-A- 0102391	14/03/84
		US-A- 4532123	30/07/85
		CA-A- 1204058	06/05/86
		US-A- 4637905	20/01/87
US-A- 4261969	14/04/81	None	